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# BORDEN'S REVIEW *of* NUTRITION RESEARCH

## *ISOTOPES IN NUTRITION RESEARCH*

### *II. Mineral Metabolism*

# BORDEN'S REVIEW
## *of*
# NUTRITION RESEARCH

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# *ISOTOPES IN NUTRITION RESEARCH*

## *II. Mineral Metabolism*

The use of isotopic tracers as a powerful investigative tool has resulted in the development of new concepts in intermediary metabolism. The most significant of these is the principle that the body constituents are in continuous dynamic equilibrium with each other and with ingested nutrients. The development and confirmation of this principle as it applies to the metabolism of the organic nutrients have already been discussed.* That this same principle holds true in the case of mineral metabolism as well has also been demonstrated. Thus, for example, even the constituents of such apparently fixed and permanent structures as the bones and teeth are known to exist in a state of constant flux, undergoing continuous, rapid breakdown and reconstruction from day to day.

The separation and concentration of stable isotopes from their naturally occurring mixtures, with the exception of the uranium isotope, $U^{235}$, (1) have been restricted to the lighter elements, especially hydrogen, carbon, nitrogen and oxygen. For this reason, the stable isotopes have found greatest application in the metabolic investigation of organic compounds, while the application of the tracer method to the heavier elements — phosphorus, iron, iodine, calcium, and others — has been confined to the use of the radioactive isotopes. The use of these radioactive isotopes has made possible significant new findings in mineral metabolism. Typical among the problems studied have been absorption, permeability, storage, distribution, chemical transformation, and paths of excretion of the mineral elements. The chief elements studied have been phosphorus, iron, iodine, sodium, potassium, and sulfur.

### *Phosphorus:*

Because of its ease of preparation, relatively long half-life (about two weeks), its fairly high intensity of radiation (making it readily detectable), and the importance of its compounds, radio-phosphorus has been the chief radioactive isotope used thus far in the study of metabolic processes. A large part of the investigations with radio-phosphorus, $P^{32}$, has been carried out by Hevesy and co-workers at the Institute of Theoretical Physics in Copenhagen. Hevesy, it will be remembered, was the first to apply the principle of radioactive tracers to the investigation of metabolism, through the use of the naturally occurring radioactive isotope of lead, radium $D^{1}$. With the availability of artificially induced radioactivity, resulting from the researches of the Joliot-Curies and of E. O. Lawrence, Hevesy, as well as other investigators, found it possible to extend the investigation of metabolism studies to other elements.

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(1) *cf—Borden's Review of Nutrition Research,* October, 1945—"Isotopes in Nutrition Research. I. The Intermediate Metabolism of Fats, Proteins and Carbohydrates."

The investigation of phosphorus metabolism was begun about ten years ago, when Chievitz and Hevesy (1a, 2, 3) by adding radio-phosphorus (as radioactive sodium phosphate) to food, demonstrated that an appreciable part of the food phosphorus rapidly found its way into the bones, teeth, muscle and other organs of both growing and adult animals. The phosphorus taken up by the skeleton during growth became equally distributed in time over the whole of the skeleton, thus demonstrating the dynamic nature of bone formation. An interesting observation was the rapid disappearance of labeled phosphorus from the blood following the injection of labeled sodium phosphate. This was interpreted as being due to the withdrawal of phosphate ions by the calcium phosphate of the skeleton — the result of the exchange of phosphate ions between plasma and bone. It was found that this interchange between plasma and bone phosphate ions occurs chiefly, as might be expected, in that part of the bone which is most vascular. For this reason a greater rate of phosphorus deposition was found in the epiphyses or growing ends of the long bones as compared to that occurring in the shafts. In a detailed study of the deposition of phosphorus in teeth, the same principle was found to operate (4). In the rat, labeled phosphate was deposited in close proximity to the vascular pulp from which it was derived and was equally distributed throughout the rapidly growing incisors. In the non-growing molars of adult rats, the accumulation of labeled phosphorus was considerably less. Three to four times as much labeled phosphorus was found in the canine teeth as in the molars of young cats sacrificed only a few hours after subcutaneous administration of the radiocompound. In adult animals the quantities were approximately the same in different teeth several days after injection. In a sixteen-year-old human subject, only about one part in 300,000 of the administered radio-phosphorus atoms enters a single tooth. It was calculated that the replacement of one per cent of the phosphorus content of a human tooth by phosphorus atoms from ingested food would take about 250 days. Similarly, it was calculated that the average time a phosphorus atom remains in the rat body is about two months (1) and in the rabbit (5) about one month. Data for humans indicate that about one-seventh of the phosphorus excreted in the feces enters the digestive tract from the blood after having been in diverse body tissues for various lengths of time (6).

Similar studies in muscle metabolism indicate that the molecules of important muscle compounds, creatine-phosphoric acid, adenosine phosphate and hexose phosphate undergo continuous breakdown and reconstruction, the rapidity of the processes being such that one day should be sufficient for their practically complete regeneration (7).

The dynamic state of brain tissue components has also been demonstrated through the injection of labeled phosphates. Hahn and Hevesy (8) isolated lecithin containing radio-phosphorus from the brains of rats, mice and

rabbits within an hour after injection of labeled material. Chaikoff *et al* (9) estimated the rate of phospholipid turnover in the brain and other organs by measuring the amount of labeled phospholipids in different tissues at various periods after ingestion of labeled sodium phosphate. The rate of turnover in the brain was lower than that in the liver, kidney or small intestine. It was greater in young animals than in old, decreasing quite rapidly from birth until maturity. In the younger rats, the spinal cord showed higher activity than the rest of the nervous system, while in the older animals the relative activities of the forebrain, cerebellum, and medulla were as great as, or greater than, that of the cord. Loofbourow (19) has speculated on the interesting possibility that such data might be obtained for humans and correlated with the development of reflexes, rate of learning and other mental processes.

Numerous other studies on the intricacies of phospholipid metabolism were conducted with radio-phosphorus by Hevesy's group, as well as by Chaikoff and associates, Artom and co-workers (10) and others. Among the most interesting of these studies is the recent work on the relation of phospholipid turnover to the formation of the pathologic condition of fatty liver. As described in previous issues of this Review,* the rate of phospholipid formation is stimulated by certain lipotropic compounds, notably choline, ethanol-amine, lipocaic and others. Reserve fats cannot be utilized until they are combined with phosphorus and thereby converted to the phospholipid form. In the absence of lipotropic compounds, either through dietary inadequacy or interference with body synthesis, fat stores accumulate and remain unused in the liver, thereby leading to fatty infiltration and degeneration of that organ.

The role of phosphorus in normal and rachitic rats, studied by means of radio-phosphorus, has offered new insight into some of the factors involved in this bone disease. Dols and co-workers (11, 12, 13) found no significant difference between rachitic and normal rats in the absorption from or re-excretion of the labeled phosphorus into the gut. They did find, however, a significant increase in lipid phosphorus in rachitic rats. From this they concluded that rickets is associated with an increased formation or a decreased destruction of phospholipids. In further studies with chicks, these workers made the interesting observation that phosphorus metabolism is more intense in rachitic than in normal animals and that metabolism of this element is more intense in the epiphyseal portion of the bone than in the shaft. The uptake of inorganic radio-phosphorus was found by Cohn and Greenberg (14) and by Manly *et al* (15, 16) to be increased by the administration of vitamin D.

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**cf—Borden's Review of Nutrition Research,* October, 1942—"Labile Methyl Groups—a New Recognized Dietary Essential" and *Borden's Review of Nutrition Research,* October, 1945—"Isotopes in Nutrition Research. I. The Intermediate Metabolism of Fats, Proteins and Carbohydrates."

One of the most interesting studies carried out with radio-phosphorus has been that of Aten and Hevesy (17) on the role of phosphorus in the formation of milk. When radioactive phosphorus, in the form of sodium phosphate, was administered to goats, it was found that in three to four hours the labeled inorganic phosphorus in the milk was almost entirely composed of labeled phosphorus which found its way into the plasma after its administration. The milk protein, casein, showed a high concentration of radio-phosphorus, from which it has been concluded that the phosphorus used in its synthesis is derived from the inorganic phosphorus of the plasma. From the rate of exchange it was estimated that the time of formation of casein in the mammary gland cells is about one hour. Ester phosphates were found to be formed more slowly than casein, while the formation of milk phosphatides was extremely slow. Similar studies on phospholipid formation in egg yolk were conducted by Hevesy and Hahn (18). Evidence of phospholipid formation appeared in the egg yolk in about five to six hours after administration of radio-phosphorus, a maximum level of deposition being reached in about twelve hours.

The use of radio-phosphorus as a means for applying local internal radiation in certain blood disorders such as leukemia and polycythemia, has met with notable success and gives promise of affording definite palliative, and possibly curative, therapy (19a, 19b).

The foregoing represent only a few highlights in the recent history of phosphorous metabolism as made possible through the use of the isotope tracer technique. These investigations are still being actively pursued in numerous laboratories with new information and new concepts being developed regarding the multitudinous phases of phosphorus activity in the living organism.

***Iron:***

Whipple and associates at the University of Rochester have pioneered in the use of radio-iron as a means for studying iron metabolism. In particular their studies have been devoted to the determination of the various factors relating to the conversion of inorganic iron to the hemoglobin of the red blood corpuscles. Prior to these studies, it had been generally assumed that the iron taken into the body in food or water was absorbed from the stomach and small intestine and that amounts in excess of normal body requirements were excreted in the lower portion of the digestive tract. This concept — that the content of iron in the body is regulated by excretion — has been entirely revolutionized by studies with radio-iron.

Using dogs as experimental animals, Hahn, Whipple and their associates (20, 21) compared the uptake of radio-iron in normal dogs with that in dogs rendered anemic by repeated bleeding and by maintenance on an iron-deficient diet. Inorganic ferric salts, labeled with radio-iron, were fed

to both groups of dogs. The animals were killed at various intervals and the radioactivity of the tissues determined with the Geiger counter. The uptake of the tagged iron was from 4.1 to 12.7 per cent in the anemic animals, while in the normal controls it ranged only from 0.08 to 0.24 per cent. Further, in the anemic dogs, most of the absorbed radio-iron was found in the red blood cells, while in the controls a much smaller proportion was deposited in these cells. These observations indicated that the uptake of iron is determined by the need of the body for iron and that in anemic animals the total absorption of iron and the relative proportion of the absorbed iron in the blood is much larger than in normal animals.

These initial studies were followed by an investigation of the metabolism of labeled iron following its injection intravenously in normal and anemic dogs (22). It was noted that the rates of elimination of the radio-iron were very slow in both groups and that no significant differences in the rate of excretion occurred. It was concluded, therefore, that the level of iron stores in the body is controlled by regulation of the amount of iron absorbed from the digestive tract rather than by any mechanism involving elimination of assimilated iron. A further interesting observation resulted from other experiments by Whipple's group (23, 24), namely that absorbed radio-iron in the blood was utilized almost entirely for the synthesis of the iron-containing protein, hemoglobin. An unusual corrollary to this observation was the discovery that ingested radio-iron is more efficiently converted into hemoglobin when the total amount administered is very small.

Factors involved in the absorption of iron were determined in an ingenious experiment, using the same animal as its own control (25). Radio-iron, in the form of a ferric salt, was fed to a normal dog and the uptake of the element determined. It was found that only 1.3 per cent of the administered material was assimilated. The animal was then rendered acutely anemic by the removal of about two-thirds of the total circulating blood. Twenty-four hours later the same dosage of radio-iron was again fed. The uptake of this dose was approximately the same as it had been before the animal was bled. Sufficient time was then allowed to elapse in order to permit the hemoglobin level of the circulating blood to be replenished to a nearly normal level — *at the expense of the body stores of iron.* Now, again, a third dose of radio-iron was administered. This time the uptake was 10 per cent as compared with less than 2 per cent in the two preceding experiments. On the basis of this evidence, Whipple *et al* suggested that the absorption of iron is not influenced by the presence of anemia *per se,* but is controlled by the degree of depletion of the iron in the tissues — and, in particular, by the amount of iron present in the cells which line the digestive tract.

The work of Whipple's group has been confirmed by the experiments of Austoni and Greenberg (25a) who investigated the absorption, excretion and

distribution of iron in rats which had been maintained on normal and iron-deficient diets. They found that approximately twelve hours were required for a single dose of radio-iron to pass through the stomach and small intestine of normal animals. In animals on iron-deficient diets, the rate of passage was considerably slower. Further, the uptake of the administered iron by the blood and tissues was greater in the anemic animals. Tissues of the normal animals contained only traces of the administered radio-iron compared to average levels of 25 per cent stored in the muscle and 14 per cent in the blood of the anemic animals at the end of ten days. These studies reemphasized the fact, pointed out by Whipple *et al,* that the absorption of iron by the body is increased if the tissues have been depleted of this element. Further, the significant fact is demonstrated that muscle tissue apparently acts as the chief storage depot for iron administered to anemic animals. In very recent work, it has been reported that the efficiency of absorption of iron in the ferrous form is considerably greater than for the ferric form (25b, 25c).

## *Iodine:*

Most dramatic of the physiological studies with radioactive tracers have been those conducted with radio-iodine. The study of iodine metabolism is intimately involved with the physiology and pathology of the thyroid gland. It has yielded some of the most dramatic results of all the physiological investigations made possible through the use of radioactive tracers. The use of radio-iodine has confirmed many of the classic concepts of thyroid function and has shed new light on heretofore unsolved problems, representing a tremendous advance in technology over previous laborious methods. Radio-iodine as a potential therapeutic tool in various thyroid pathologies constitutes a story of such interest that, although much of it is beyond the scope of this Review, it is considered worthwhile to touch upon some of the highlights of this work.

The thyroid gland is unique among all the body tissues in its ability to absorb selectively large quantities of a particular element. The affinity of this gland for iodine is such that the concentration of iodine in thyroid tissue is about one part in a thousand as compared with less than one part in five million for other body tissues. Iodine in the thyroid has been discerned in three distinct forms, inorganic iodide, the iodinated amino acid, di-iodotyrosine, and the hormone, thyroxine.* Investigations with radio-iodine have served to clarify the significance of these three iodine-containing fractions.

The first physiological experiments with radio-iodine were carried out by Hertz (26, 27) and Hamilton (28, 29, 30) and their co-workers. They measured the rate of uptake of radio-iodine by the thyroid and demonstrated

*cf—*Borden's Review of Nutrition Research,* September, 1943—"Iodine in Nutrition."

that this occurs with great rapidity. By placing a Geiger counter for detecting radiations on the neck of a patient directly over the thyroid, it was possible to conduct studies without the need for surgery. By this means, for example, it was found that five minutes after a patient had swallowed a solution of radio-iodine, the Geiger counter recorded the presence of the radioactive material in the thyroid (31). On the basis of characteristic curves of the uptake of radio-iodine it was possible further to distinguish among various types of thyroid dysfunction such as toxic and non-toxic goiter, hypothyroidism, and others. Insight into the mechanisms of these dysfunctions was afforded through observations on the rate of loss of radio-iodine from the thyroid following its initial uptake (29). For example, the toxic goiter was found to replenish its stores of iodine and immediately pour it forth as the newly made hormone, thus aggravating the existing hyperthyroid state. In hypothyroidism with non-toxic goiter, the newly trapped iodine was soon released, apparently as thyroxine, to restore normal metabolic levels. Normal and hyperplastic (but non-toxic) glands merely trapped and stored iodine to capacity. Such studies as these have potential value for providing diagnostic techniques in distinguishing abnormal thyroid activities.

The normal metabolic pathway of ingested iodine was followed in animals as well as in humans by Morton, Chaikoff *et al* (32). They demonstrated the existence in the thyroid of the three iodine-containing fractions, thereby confirming earlier hypotheses that the gland traps inorganic iodide which is utilized for the iodination of tyrosine, an intermediate in the eventual formation of the iodine-containing hormone, thyroxine. The formation of di-iodotyrosine and thyroxine *even in completely thyroidectomized animals* was demonstrated by these same workers (33) with radio-iodine. This synthesis of thyroxine by tissues other than the thyroid leads to interesting speculations concerning the role of thyroxine in the body.

The recent discovery that the compounds, thiourea and thiouracil, are effective in controlling hyperthyroidism has also led to interesting contributions to the theories of thyroxine formation. Using radio-iodine, Keston, Goldsmith, Gordon and Charipper (34) found that in the presence of thiourea, ingested iodine does not lead to thyroxine formation. It has been postulated that the action of thiourea is to prevent the *in vivo* formation of free iodine which is necessary for organic iodination. Similar evidence indicating the importance of free iodine in essential biological iodinations has been reported by Keston (36) in studies with the Schardinger enzyme of milk.

The selective accumulation of radio-iodine by the thyroid gland and the high specific activity of this material make it possible to secure local high intensity radiation of the gland. Advantage has been taken of this fact in attempts to treat thyroid carcinoma with radio-iodine. Such treatment is restricted to a particular type of thyroid cancer in which the malignant tissue has retained its characteristic ability to fix iodine. (This ability is usually

lost in more common types of thyroid cancer.) Keston *et al* (34a, 35) have applied such direct radiation therapy in this type of cancer in an attempt to check the growth of the malignant tissue in the thyroid itself or in metastases to other parts of the body.* The authors point out that long-term observations on a considerable number of patients thus treated — and also further experimental work — are essential before their work can be fully evaluated.

## *Other Minerals:*

Radioactive isotopes of sodium, potassium, fluorine, calcium, strontium and other mineral elements have also been employed for physiological investigations. Labeled sodium and potassium have elucidated questions concerning cell permeability to these ions and have given a possible explanation for some of the phenomena occurring in shock (37, 38, 39). Radio-fluorine has served to confirm recent theories concerning the role of fluorine in the prevention of dental caries (40).** The absorption, distribution and excretion of calcium, manganese, copper and other mineral elements have been followed by means of their radioactive isotopes. Because of their selective deposition in bone, the possibility of therapy with radio-calcium and radio-strontium has suggested itself for the treatment of bone sarcomas.

## *Conclusion:*

Radioactive isotopes have made possible new insight into the intricacies of mineral metabolism, being particularly useful in the fields of clinical investigation and therapy. Radioactive iodine and phosphorus especially have been used extensively, both to follow the biological fate of these elements and to provide sources of local radiation in the tissues (thyroid and blood, respectively) which fix these elements preferentially. Metabolism under abnormal conditions as well has been explored with the aid of radioactive tracers as, for example, the fate of iron in anemia or iodine in thyroid dysfunction.

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*The ability of these metastases (cancer cells which have migrated to other parts of the body) to fix iodine in much the same manner as normal thyroid tissue—even though they may be located in bone, muscle, or other tissues, has made possible their accurate location with the Geiger counter.

**cf—*Borden's Review of Nutrition Research*, December, 1942—"Fluorine and Dental Health."

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# *NEWS DIGEST*

**ENRICHED FLOUR** — Whether or not a commercial flour has been enriched with niacin can now be detected almost instantly by means of a simple chemical test recently developed. The test requires the use of two reagents and a small quantity of the flour to be tested. The flour sample (about ½ to 1 gram) is pressed on a white blotter or in a laboratory porcelain indicator block and two drops of the first reagent are applied. This is followed by three drops of the second reagent. The resulting yellow color and its various degrees of depth relative to that of certain control tests indicate the degree of enrichment with niacin, or lack of it. Comparison of color must be made within four minutes of the application, however, because even unenriched flour will take on a certain amount of color in due course, from the amount of niacin, however small, naturally present. *Chem. and Engin. News 23,* 604 (1945).

**HIGH VITAMIN RICE** — The rapid production of a rice of high food value has recently been perfected through the use of a machine developed at one of the State agricultural universities. The machine peels the rice rapidly in one operation, removing the husks but permitting retention of most of the germ and bran layers. The vitamin content of the rice is of about the same order as that of unpolished or brown rice. The rice itself is not quite as white as ordinary polished rice, and is said to keep as well as unpolished rice. *Food Field Reporter,* Feb. 19, 1945.

**FRESH BREAD** — Bread that will remain fresh for about three weeks or longer has been developed in Canada for use by sailors at sea. The new type of bread is characterized by the addition of 8% soy flour in the usual bread mixture, and a small decrease in the quantity of shortening. The use of soy flour in cake batters is now being investigated in order to determine what proportions are necessary to keep cakes similarly fresh at sea. *Canadian Home Economics Newsletter,* June, 1945.

**PRE-DIGESTED FOOD** — As an immediate emergency measure, liberated European countries are being supplied with special pre-digested foods designed for intravenous administration. Use of these foods will restore victims of extreme starvation so rapidly that they may be able to take small quantities of ordinary foods within 24 to 28 hours after administration of the pre-digested foods. The special foods consist of glucose, pre-digested proteins and fats, and vitamins. *Food Field Reporter,* June 11, 1945.

**GERIATRIC FOOD** — The growing importance of geriatrics as a specialized field of study has emphasized the significance of foods and nutrition as primary factors in maintaining the health and well-being of older persons. Keyed to the demand for special purpose foods designed for this age group, is a recently developed food product consisting of a powdered milk base scientifically fortified with vitamins and minerals. Two eight-ounce glasses daily provide for the adult daily minimum requirements of all vitamins and minerals and also provide important milk fat, protein and carbohydrate. The product may be flavored to suit taste and may be reconstituted as a beverage or used in cookery. *New York World Telegram,* Aug. 8, 1945.